REMARKS

Claim Status

Reconsideration of this application is respectfully requested. Claims 11, 12, and 21 have been amended to additionally depend from claim 23. Claims 10 and 23 have also been amended to more particularly point out and distinctly claim the subject matter that Applicants wish to prosecute in this application. Claims 10 and 23 have been amended to recite "consisting of" rather than "comprising." Additionally, in claim 10 the phrase "or 2" has been cancelled. Applicants expressly reserve the right to pursue any cancelled subject matter in subsequent applications that claim benefit from this application.

No new matter has been introduced. Claims 10-15 and 21-23 are pending and at issue.

Claim Rejection - 35 U.S.C. §103

Claims 10-15, and 21-23 stand rejected under 35 U.S.C. § 103(a) as allegedly being obvious over U.S. Patent No. 6,866,849 (hereafter "the '849 patent") in view of Ghanta et al., 1996, *J. Biol. Chem.*, 271(47): 29,525-29,528 (hereafter "Ghanta"), U.S. patent no. 6, 962,707 (hereafter "the '707 patent"), Maillere et al., 1995, *Molecular Immunology*, 32(17/18): 1377-1385 (hereafter "Maillere"), Yankner et al., 1990, Science, 250(4978):279-282 (hereafter "Yankner"), Solomon et al., 1997, PNAS, 94:4109-4112 (hereafter "Solomon"), and Pike et al., 1993, J. Neuroscience, 13(4):16786-87 (hereafter "Pike"). The Examiner contends that the claimed peptides would have been obvious to one of skill in the art because they are the result of combining known elements from known methods to yield predictable results. These grounds for rejection are not well taken and are respectfully traversed.

The peptides called for in the present claims are based upon SEQ ID NO: 1 with the modifications as described:

An isolated peptide comprising the amino acid sequence:

(Asp Ala Glu Phe Arg His Asp Ser Gly Tyr Glu Val His His Gln Lys Leu Val Phe Phe Ala Glu Asp Val Gly Ser Asn Lys Gly Ala)$_n$ (SEQ ID NO:1)

wherein n is 1 or 2; and

wherein the isolated peptide further comprises an N-terminal, C-terminal, or both N- and C-terminal, polylysine or polyaspartate sequence of 4-10 residues.

The pending claims also encompass a method for using the claimed Aβ peptides to mount an immune response to amyloid β (hereafter "Aβ") peptides and amyloid deposits. *No combination of the cited references teaches or suggests the combination of uses and features, called for in the pending claims.*

The present claims are rejected on the combined teachings of seven (7) different references. In making this rejection the Examiner has chosen selected teachings from seven different references to support the argument that the present claims are obvious. It is evident the Examiner is using impermissible hindsight to reconstruct the invention called for in the present claims by picking and choosing elements from among seven prior art references. The Examiner fails to provide a reason that would have prompted a skilled worker to combine the discrete elements in the cited prior art to arrive at the claimed peptides because the reason is found in the teachings of the present application. Such hindsight reconstruction has been condemned in the courts. *See In re Fine*, 837 F.2d 1071, 1075, 5 USPQ2d 1596, 1600 (Fed. Cir. 1988) ("One cannot use hindsight reconstruction to pick and choose among isolated disclosures in the prior art to deprecate the claimed invention"); *In re Fitch*, 23 USPQ2d 1780, 1784 (Fed. Cir. 1992). As detailed in the comments below, the Examiner has failed to establish *prima facie* obviousness on these grounds as well. *See Symbol Techs., Inc. v. Opticon, Inc.*, 935 F.2d 1569 (Fed. Cir. 1991) ("We do not 'pick and choose among the individual elements of assorted prior art references to recreate the claimed invention,' but rather, we look for 'some teaching or suggestion in the references to support their use in the particular claimed combination.'").

At the outset, Applicants point out that a skilled worker would not have been able to predict the precise manner in which the elements that the Examiner points to in the seven pieces of prior art, and that are discussed in the following comments, should have been combined to arrive at the claimed peptides. In fact, this is evident from a reading of the current application, specifically Figures 2A and 2B, as filed. The present inventors assessed the safety of vaccination (*i.e.*, assessed the level of neurotoxicity) with Aβ having six lysine (K6) residues at the N-terminus or at the C-terminus. The number of viable human neuroblastoma cells (SK-N-SH) after 2 days (Figure 2A) and after 6 days (Figure 2B) following treatment with Aβ1-30, Aβ1-30 with K6 at the N-terminus, Aβ1-30 with K6 at the C-terminus is different. In fact, the 100 μM Aβ1-30 with K6 at the C-terminus treatment appeared to be slightly toxic compared to the same concentration of Aβ1-30 or Aβ1-30 with K6 at the N-terminus. This demonstrates that modification of Aβ1-30 as called for by the pending claims does not yield a predictable variation of any of the elements identified by the Examiner in the cited prior art.

The Examiner relies upon the '849 patent as the primary reference for his obviousness rejection. The '849 patent discloses administration of a peptide consisting of the first 39 amino acids of natural amyloid β (hereafter "Aβ1-39") for evoking a therapeutic antibody response. The '849 patent does not disclose polylysine or polyaspartate modifications, as called for by the present claims, to the natural Aβ1-39 fragment. Moreover, the '849 patent does not teach or suggest the synthetic Aβ peptides defined by the instant claims as described above. Nonetheless, the Examiner attempts to cure the deficiencies of the '849 patent with the six other prior art references.

The Examiner relies upon Ghanta for teaching that Aβ15-25 with lysine hexamers acts as an inhibitor of toxicity, and for using Aβ1-39 as a positive control for Aβ toxicity in studies aimed at identifying inhibitors of toxicity. The Examiner contends that it is predictable that lysine hexamers as taught by Ghanta would be effective in inhibiting the toxicity of Aβ1-30, but offers no evidence to support this contention.

For the reasons set forth above, even with Ghanta in hand one of ordinary skill would have been unable to predict that the peptides called for in the present claims would have a lowered risk of toxicity.

The N-terminal Aβ peptides of the present claims are not suggested by the internal Aβ peptides taught by Ghanta, Aβ peptide fragments comprising internal amino acids of full length Aβ are not the same as fragments comprising the N-terminus 1-30 amino acids of full length Aβ. A skilled worker would not have expected that an internal peptide fragment of Aβ would have the same properties as an N-terminal Aβ peptide fragment. And as such, a skilled worker would not have been motivated by the internal Aβ peptides taught by Ghanta to prepare the N-terminal Aβ1-30 peptides as defined by the present claims.

The claimed Aβ peptides are also distinguishable from the Ghanta peptides because the claimed Aβ peptides are immunogens, not inhibitors. Ghanta does not describe or suggest use of the inhibitor fragments as immunogens. Importantly, the person of ordinary skill in the art would have had no reasonable expectation that an inhibitor could serve as an immunogen. Neither Ghanta nor any of the six prior art references teach or suggest to a skilled worker that a peptide that is useful as an inhibitor can serve as an immunogen. The use of an inhibitor, or an inhibitor with a modification, as an immunogen would have required experimentation; it is not a result that a skilled worker would have been able to predict. Thus, Ghanta fails to cure the deficiencies of any of the other six pieces of prior art.

The Examiner states that Yankner shows that it is predictable that the claimed peptides would have the advantage of lowered risk of toxicity to human beings compared to Aβ1-42. The Examiner relies upon Yankner for teaching that Aβ1-38 and Aβ1-40 have high toxic activity, and that the toxicity of Aβ1-28 is greatly reduced relative to Aβ1-40.

Yankner does not disclose or suggest toxicity data for Aβ1-30 with polylysine or polyaspartate modifications as called for by the present claims. In particular Yankner does not suggest an N-terminal Aβ1-30 fragment (either one fragment of 30 amino acids or two fragments of 60 amino acids) that also requires a polylysine or polyaspartate sequence of 4-10 residues at the N-terminal, C-terminal, or both the N- and C-terminal ends, as called for in the present claims. As discussed in the foregoing comments, the present inventors have demonstrated that the modifications of Aβ1-30 as called for by the pending claims do not yield a predictable variation of

the elements identified by the Examiner in the cited prior art references much less Yankner considered on its own.

The Examiner states that the '707 patent teaches a therapeutic agent comprising polylysine or polyglutamic acid linked to the amino or carboxyl terminus of an immunogenic, natural Aβ peptide, and that polylysine and polyglutamic acid are identified as immunostimulatory molecules. The Examiner also states that the '707 patent teaches immunization with multimers. The Examiner also states that the '707 patent teaches Aβ peptides for which high antibody titers were obtained because immunogeneic sequences are found within Aβ1-12 and Aβ13-28.

The teachings in '707 patent, tables alone or in combination with the teachings in the '849 patent, or any of the other five prior art references, do not provide guidance to a skilled worker for modifying Aβ peptides with polylysine or polyaspartate at the N-terminal, C-terminal, or both the N- and C-terminal ends. First, the '707 patent does not disclose or suggest addition of polylysine or polyglutamic acid to the amino or carboxy terminus of the therapeutic agent. The specific location for the addition of polylysine or polyaspartate to the amino or carboxy terminus is disclosed in the current application, not in the prior art. The '707 patent merely states that polylysine or polyglutamic acid may be used as adjuvants, but does not specify how (or where) it should be used.

Second, the '707 patent does not teach or motivate a skilled worker to combine the prior art elements to successfully arrive at the claimed Aβ peptides because the claimed peptides are not a predictable variation of the '707 teachings. At the time of the present invention, the '707 patent, alone or in combination with the other cited prior art, lacked the guidance to lead the skilled worker to make or use the claimed peptides comprising an N-terminal Aβ1-30 fragment (either one fragment of 30 amino acids or two fragments of 60 amino acids) that also requires a polylysine or polyaspartate sequence of 4-10 residues at the N-terminal, C-terminal, or both the N- and C-terminal ends. As discussed in the foregoing comments, the modifications of Aβ1-30 as called for by the pending claims do not yield a predictable variation of any of the elements identified by the Examiner in the cited prior art.

Lastly, the '707 patent does not contain a teaching or suggestion from which a skilled worker would have reasonably expected that the net benefit of combining the immunogeneic sequences within Aβ1-12 and Aβ13-28 would have resulted in an N-terminal Aβ peptide useful as an immunogen as required by the pending claims.

The Examiner contends it is predictable that any peptide comprising the first 28 amino acids of Aβ should evoke production of antibodies (see Office Action at pg. 4) and further argues, Solomon teaches antibodies raised against Aβ1-28 causing disaggregation of Aβ fibrils and inhibit the neurotoxicity of Aβ. The Examiner's reading of Solomon is simply not correct.

Solomon does not disclose antibodies raised against Aβ1-28 in its entirety. Rather, Solomon discloses monoclonal antibodies (mAb) 6C6, mAb 1C2, and 14C2, all of which are raised against discrete Aβ fragments within Aβ1-28. The mAb 6C6 recognizes the epitope located on the region of Aβ1-16. The mAb 1C2 was raised against the region of Aβ13-28. The mAb 14C2 was raised against the region of Aβ33-40. These Aβ regions taught by Solomon are the same as those taught by the '849 patent and the '707 patent because the mAbs used in Solomon were provided by D.Schenk the named inventor of the '849 and '707 patents. Thus, Solomon does not teach that it is predictable that any peptide comprising the first 28 amino acids of Aβ will elicit an immune response, much less the particular features of the claimed Aβ peptides.

The Examiner relies upon Pike for the teaching that Aβ1-28, Aβ1-30, and Aβ1-33 each show little toxicity to neurons in culture to illustrate that it was well known that toxicity is greatly diminished by omission of amino acids from the C-terminus of Aβ.

Pike does not teach or suggest Aβ1-30 with polylysine or polyaspartate. Specifically, the present claims require Aβ1-30 (either one fragment of 30 amino acids or two fragments of 60 amino acids) and polylysine or polyaspartate at the N-terminal, the C-terminal, or both N-and C-terminal ends.

The Examiner states that Maillere teaches that amidation of the C-terminus of an administered peptide decreases proteolytic degradation of peptides, thereby enhancing the capacity of the peptide to activate lymphocytes. Based upon Maillere, the Examiner states that "the skilled

artisan seeking to evoke an immune response to Aβ peptides would expect that C-terminal amidation would be an advantageous modification."

The Examiner attempts to cure the deficiencies of the cited prior art discussed above with Maillere. However, nothing in Maillere, alone or in combination with the other six cited prior art references, describes or suggests the claimed Aβ peptides.

As set forth above, the Examiner is using impermissible hindsight reconstruction in rejecting the present claims under the guise of obviousness. In making the obviousness rejection the Examiner is impermissibly picking and choosing unrelated elements from among the '849 patent, Ghanta, the '707 patent, Maillere, Yankner, Solomon, and Pike to reject the claimed peptides as obvious. The Examiner provides no reasons as to why one skilled in the art would have combined the teaching of seven disparate references to arrive at the present claims. The differences between the prior art and the pending claims are significant because the prior art provides no guidance or expectation of success for making or using the Aβ peptides as called for by the present claims; and the level of ordinary skill in this art is relatively high. *See KSR Int'l Co. v. Teleflex Inc.*, 127 S. Ct. 1727, 1734 (2007); *Graham v. John Deere Co. of Kansas City*, 383 U.S. 1, 15-17 (1966). The guidance that is missing in the seven prior art references is found in the teachings of the present invention. It is the present specification not the prior art that teaches the composition of the present claims. It is only by picking and choosing unrelated teachings from seven different prior art references that the Examiner is able to synthesize reasons for rejecting the present claims for obviousness. As set forth above, this practice has consistently been condemned by the courts.

As discussed in the foregoing comments, reasons are provided why one of ordinary skill in the art, even if so motivated, would not have been able to predict the success of combining the claimed elements to successfully arrive upon the Aβ peptides as claimed. The mere fact that references can be combined or modified does not render the resultant combination obvious unless the prior art also suggests the desirability of the combination. *In re Mills*, 916 F.2d 680, 16 USPQ2d 1430 (Fed. Cir. 1990). The particular features of the claimed Aβ peptides as described in the foregoing comments establish that it would not have been within the technical grasp of a skilled

worker to predict a likelihood of success for making or using the claimed Aβ peptides by combining discrete elements of the cited prior art, each alone or in combination.

At best, the seven cited references provide only an invitation to experiment further, which is insufficient to establish obviousness in the context of unpredictable results. Determining the various elements that can be combined to make a peptide suitable as an immunogen to elicit a desired immune response requires experimentation and is unpredictable until a peptide of that type is made and tested. It was only through experiments carried out by the present inventors as described in the specification that the parameters for the inventive peptides were determined and tested. MPEP § 2145(X)(B); *In re Dow Chemical Co.*, 837 F.2d 469 (Fed. Cir. 1988); *see also Ecolochem, Inc. v. Southern California Edison Co.*, 227 F.3d 1361 (Fed. Cir. 2000) ("'obvious to try' is not the standard").

Finally, this conclusion is consistent with the Supreme Court decision *KSR v. Teleflex*, 127 S. Ct 1727 (2007)[1] where in contrast to the presently claimed peptides, the court discussed *predictable* outcomes that support a finding of obviousness stating:

> The combination of familiar elements according to known methods is *likely to be obvious when it does no more than yield predictable results*." (emphasis added) (discussing *United States v. Adams*, 383 U.S. 39, 40 (1966) (the companion case to *Graham*), *Anderson's Black Rock, Inc. v. Pavement Salvage Co.*, 396 U.S. 57 (1969), and *Sakraida v. AG Pro, Inc.*, 425 U.S. 273 (1976)).

For at least the reasons set forth above, pending claims 10-15, 21-23 are not obvious over the prior art of record. Reconsideration of the claims and withdrawal of the rejections under 35 U.S.C.§ 103(a) is respectfully requested.

[1] Holding that *Graham v. John Deere* controls the obviousness inquiry and warning that a rigid application of the teaching / suggestion / motivation test as a litmus test for obviousness is inconsistent with the *Graham* framework.

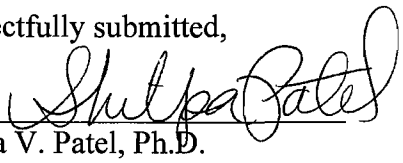
CONCLUSION

In view of the above amendments and remarks, it is respectfully requested that the application be reconsidered and that all pending claims be allowed and the case passed to issue.

If there are any other issues remaining that the Examiner believes can be resolved through either a Supplemental Response or an Examiner's Amendment, the Examiner is respectfully requested to contact the undersigned at the telephone number indicated below.

Dated: January 29, 2008

Respectfully submitted,

By 

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